

Review article

Townes-Brocks syndrome

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Abstract

Townes-Brocks syndrome (TBS) is an autosomal dominant disorder with multiple malformations and variable expression. Major findings include external ear anomalies, hearing loss, preaxial polydactyly and triphalangeal thumbs, imperforate anus, and renal malformations. Most patients with Townes-Brocks syndrome have normal intelligence, although mental retardation has been noted in a few.

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The gene for Townes-Brocks syndrome was mapped to 16q12.1 through identifying subjects with TBS and cytogenetic abnormalities.¹⁻⁴ Mutations in a candidate gene, SALL1, have been found in one family and in an isolated case with typical features of this syndrome.⁵

Townes-Brocks syndrome is an autosomal dominant multiple malformation syndrome characterised by external ear malformations with sensorineural hearing loss, thumb anomaly,

lies, and anorectal malformation. Intelligence is usually normal, although mild-moderate mental retardation has been reported.^{6,7} Townes and Brocks first described the syndrome in 1972.⁸ Since that time over 65 cases have been published^{1-3,5-21} (table 1).

Diagnostic criteria suggested for TBS include two or more of the following: (1) anorectal malformation (imperforate anus, anteriorly placed anus, anal stenosis); (2) hand malformation (preaxial polydactyly, triphalangeal thumb, bifid thumb); (3) external ear malformation (microtia, "satyr" or "lop" ear, preauricular tags or pits) with sensorineural hearing loss; (4) a relative with the syndrome.²² REAR syndrome (renal-ear-anal-radial) has also been a term used to describe this condition.¹⁰

Clinical features

EAR ANOMALIES/HEARING LOSS

External auricular anomalies in TBS typically include small ears with an overfolded superior helix and small anthelix, sometimes cupped, with preauricular tags (fig 1). Other descriptive terms reported for ear shape include "satyr" and "lop". Hearing loss is common in TBS, ranging from mild to profound. It is usually

Table 1 Summary of familial and isolated Townes-Brocks syndrome cases previously reported*

Reference	No of patients	Sex	Ear anomaly	Hearing loss	Thumb anomaly	Imperforate anus	Genital-renal anomaly	Cardiac anomaly	Develop delay/MR	Other abnormalities
Familial										
8	6	3M/3F	6	4	4	5				Toe
9	19	12M/7F	5		5	4				
10	9	5M/4F	6	1	1	2	4			
1	2	1M/1F	2			2				Chromosome
11	2	2F	2	2	2	2	1			
12	2	2M	1	2	2	1	2			Toe
6	3	1M/2F	3	3	2	1	1		1	Scoliosis, CN
13	6	3M/3F	5	6	5	3	3			Eye, toe
5	3	1M/2F	3	3	3	3				
Isolated										
14	1	F	1	1	1	1			1	
15	1	M	1	1	1	1	1	1		CN
11	1	F	1		1		1	1		
16	1	F	1	1	1	1		1		
17	1	M	1		1	1		1		CN
6	1	F	1	1	1		1		1	Scoliosis
18	1	F	1	1	1			1		Toe
2	1	F	1		1	1	1			Chromosome
3	1	M	1	1	1	1			1	Chromosome
19 (case 2)	1	F	1			1		1	1	
7	1	M	1	1	1		1		1	Scoliosis
20	1	F	1		1					
21	1	M	1	1	1		1			Toe
5	1	M	1		1	1	1	1		
Total	66	34M/32F	47	29	37	31	18	7	6	

CN = cranial nerve.

MR = mental retardation.

*A detailed table of clinical features of each reported patient is available from the corresponding author.

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Figure 1 Dysplastic ear with preauricular tag and cheek tag in a child with Townes-Brocks syndrome.



Figure 2 Preaxial polydactyly and bifid distal phalanx of thumb with ulnar deviation in a patient with Townes-Brocks syndrome.

congenital and primarily sensorineural, although a small conductive component is often present. At least in some patients it is progressive, and is worse in the high frequencies.¹³ Structural middle ear anomalies have been reported and include hypoplastic malleus head and abnormally shaped oval window and incus.¹⁶

LIMB DEFECTS

The most common limb malformations are triphalangeal thumb and preaxial polydactyly with a well formed or vestigial digit. Bifurcation, ulnar deviation, or broad appearance of the distal phalanx of the thumb are also common (figs 2 and 3). Finger syndactyly has been reported in some patients with TBS. Toe anomalies occur less frequently than thumb anomalies but those described include short third toe/metatarsal, overlapping toes (typically second and fourth overlapping third), syndactyly of the third and fourth toes, and absent third toe (fig 4, table 1).

Hypoplasia of the thumb and radial bone abnormalities are not features of TBS and should raise the likelihood of an alternative diagnosis in isolated or familial cases. Reports of TBS in patients with hypoplastic thumbs and radial anomalies probably do not represent true TBS.²³ Thumb or radial hypoplasia with imperforate anus in isolated cases is more likely to be VATER association, although it is important to rule out other diagnoses (see below).

ANAL ANOMALIES

The most common anal anomaly reported is imperforate anus, varying in degree from a skin

covered opening to more severe grades of imperforation (fig 5). There is often a rectovaginal or rectourethral fistula. Anal stenosis without imperforate anus has also been reported. Excess perianal skin was also noted in several members of a large kindred with probable TBS reported by Reid and Turner.⁹

GENITOURINARY ANOMALIES

A high incidence of genitourinary abnormalities is found in TBS. These include unilateral or bilateral hypoplastic or dysplastic kidneys, renal agenesis, multicystic kidney, posterior urethral valves, vesicoureteral reflux, and meatal stenosis.^{10-12 21} In eight reported patients renal failure or impaired renal function was present.^{6 11-13 21} Several patients have had renal transplantation.^{13 21 24} This underscores the need for renal imaging and monitoring of renal function in TBS patients.

A prominent midline perineal raphe or bifid scrotum or both is common in males with TBS. Hypospadias has also been reported.^{1 12 13 15}

DEVELOPMENT

As noted above, mental retardation is not typically associated with TBS. Walpole and Hockey¹⁴ described a 29 year old female patient with typical features of the syndrome with severe behavioural problems and mild intellectual handicap. This was attributed to late diagnosis (aged 6) of her hearing loss. Cameron *et al*⁶ described two children with Townes-Brocks syndrome with mental retardation. One was a 9 year 8 month old female with ear anomalies, anteriorly placed anus, and supernumerary thumb. She had mild mental retardation (full scale IQ of 60). The second was an unrelated 14 year old male with a positive family history of TBS. He had an imperforate anus, small ears with preauricular tags, and normal thumbs. He had moderate mental retardation (full scale IQ of 47). Although his mother and sister also had features of TBS with thumb anomalies, both had normal intelligence. A 4 year 11 month old patient with imperforate anus, ear anomalies and deafness, a hypoplastic thumb, and a developmental quotient of 54 was described by Ishikiriya *et al*.⁷ These patients had normal chromosomes. Michaelis *et al*⁸ reported a boy with TBS and profound mental retardation, who had a deletion that included the distal portion of 16q12.1 and part or all of 16q13. It is most likely that this patient's mental retardation results from disruption of a gene distal to the TBS gene. Several genes capable of influencing brain development reside in the distal portion of this deleted region, including the genes encoding the noradrenaline transporter (SLC6A2) at 16q12.2, guanine nucleotide binding protein (GNAO1) at 16q13, and metallothionein 3 (MT3) located at 16q13.

HEART DEFECTS

Although congenital heart defects have been described in some sporadic cases of Townes-Brocks syndrome, as pointed out by O'Callaghan and Young,²⁵ none has been reported in familial cases. The true association of congenital heart defects with TBS has not



Figure 3 Ulnar deviation of distal phalanges of the thumbs in a patient with Townes-Brocks syndrome.



Figure 4 Second and fourth toes overlapping third and fifth toe clinodactyly in a patient with Townes-Brocks syndrome.

been proven. Hersch *et al*¹⁵ described an 8 year old male with typical TBS features and tetralogy of Fallot (TOF). Another patient with typical TBS features and TOF was described by Parent *et al*.¹⁹ Barakat *et al*¹¹ reported a 15 day old female with microtia, preauricular tags, cupped ears, triphalangeal thumbs, an anteriorly placed anus, and bilateral renal hypoplasia who had a truncus arteriosus and ventricular septal defect. Kotzot *et al*¹⁸ described a 14 month old female with "satyr" ears, preaxial polydactyly and triphalangeal thumb, and missing third toe who also had a ventricular septal defect (VSD) and pulmonary atresia. There have been other patients with TBS and VSD reported,^{16 17} and the sporadic case of Kohlhasse *et al*⁶ with SALL1 mutation (see below) had an atrial septal defect.

EYE ABNORMALITIES

Bilateral or unilateral VIth nerve palsy has been noted in two patients with other features consistent with TBS.^{6 15} Bilateral colobomata (unspecified type) were reported in one of the family members with TBS reported by Rossmiller and Pasic.¹³ Eye abnormalities are not



Figure 5 Imperforate anus in a female infant with Townes-Brocks syndrome.

common in TBS and the possibility that the reports of them in TBS patients is coincidental cannot be discounted.

SPINE ABNORMALITIES

Scoliosis has been reported in three patients with TBS. Interestingly these were three patients who also had mental retardation.^{6 7} Except for a male with familial TBS, mental retardation, scoliosis, and spina bifida occulta⁶ (a common anomaly in the general population), no TBS patients have had structural vertebral abnormalities. This helps to differentiate TBS from VATER association and syndromes with similar hand and anal malformations.^{26 27}

Differential diagnosis

Townes-Brocks syndrome features overlap those seen in several other syndromes and associations. Among these is VATER association, although Townes-Brocks syndrome does not have tracheo-oesophageal fistula or vertebral anomalies, and TBS has ear anomalies and deafness which are not typical of VATER. VACTERL with hydrocephalus, reported as an X linked or autosomal recessive condition, may include radial and renal anomalies and imperforate anus along with other VATER features.²⁸ Differentiating this condition from TBS is critical because of the different inheritance patterns and the fact that some of these patients have Fanconi anaemia²⁹⁻³¹ (C M Powell, personal observation). Although radial and thumb aplasia or hypoplasia are most commonly reported, supernumerary and bifid thumbs have also been noted in patients with Fanconi anaemia,^{32 33} as have ear anomalies/hearing loss. It is important to perform testing for sensitivity to diepoxybutane (DEB) to investigate the possibility of Fanconi anaemia in patients with these features.

There are overlapping features in TBS and Baller-Gerold syndrome, including thumb anomalies (usually absent or hypoplastic in Baller-Gerold syndrome), imperforate anus, and urogenital anomalies. An important differentiating feature is craniosynostosis which is present in 100% of patients with Baller-Gerold syndrome.³⁴

Oculoauriculovertebral spectrum (OAV) also has similar features to TBS, but again there are no vertebral anomalies in Townes-Brocks syndrome and imperforate anus is rare in OAV. An interesting family illustrating the common features of TBS and OAV was reported by Johnson *et al.*³⁵ This three generation family had external ear anomalies and preauricular tags, hearing loss, triphalangeal thumbs and preaxial polydactyly, and redundant anal skin/imperforate anus. OAV spectrum features included epibulbar dermoids, micrognathia, and macrostomia. A similar family was described by Moeschler and Clarren,³⁶ in which a mother and daughter had ear tags and pits, mandible asymmetry, triphalangeal and duplicated thumbs, and hearing loss. The daughter also had macrostomia. Gabrielli *et al.*³⁷ reported a sporadic case. Friedman *et al.*³⁸ reported a father and daughter with imperforate anus and ear anomalies and inversion of chromosome 16 presumed to be in the TBS region (see below). In addition to preauricular and cheek tags, the daughter also had macrostomia or cleft of the right oral commissure (C M Powell, personal observation), a feature often associated with OAV.

Cat eye syndrome secondary to an inverted duplication marker chromosome 22 is associated with preauricular tags and imperforate anus, but not thumb anomalies as in Townes-Brocks syndrome. A syndrome reported by Say and Gerald²⁶ includes polydactyly and imperforate anus, but unlike TBS, these patients also had tracheo-oesophageal fistula and vertebral anomalies. Preaxial polydactyly has been noted in patients with microscopic and submicroscopic deletions in the 22q11.2 region who have features of DiGeorge syndrome including external ear malformations³⁸⁻³⁹ (C M Powell, personal observation). Other syndromes with imperforate anus and features which may overlap with TBS include FG syndrome and Pallister-Hall syndrome.

There have been patients described with typical TBS features and unusual associated findings. Recently, Yano *et al.*⁴⁰ described a 10 year old boy with an anomalous left ear, mild sensorineural hearing loss, preaxial polydactyly, anal atresia, prominent perineal raphe, and chronic renal failure. He had congenital hypothyroidism and studies suggested an organification defect. Although the authors suggest that this is Townes-Brocks and Pendred syndrome in the same patient, more likely is the possibility of TBS with coincidental congenital hypothyroidism.

In reviewing the variable phenotype in familial and isolated cases of TBS, Aylsworth⁴¹ suggested that TBS was one member of the anus-hand-ear family of syndromes and that there were several reports of unique syndromes

having these features but not typical of TBS. Among these are the patients described by Silver *et al.*⁴² and Monteiro de Pina-Neto.²³

Variability

Intrafamilial variability of TBS has been established. A patient with imperforate anus, triphalangeal thumb, satyr ears, and urogenital anomalies had a father with a thumb anomaly (triphalangeal and malformed distal phalanx) but no ear or anal anomalies.¹² In a four generation family with 10 affected subjects reported by Burke and Gross, originally described by Kurnit *et al.*¹⁰ all 10 affected subjects had at least two of the four anomalies (anal, ear, renal, thumb). Anal defects were present in eight, external ear anomalies in seven, sensorineural hearing loss in seven (all with hearing loss had ear anomalies), and thumb anomalies were seen in eight. Five of the 10 had renal or urinary tract anomalies. Three members of this family required renal transplant because of vesicoureteric reflux.²⁴

Although variable expressivity is common in TBS, there are no convincing reports of incomplete penetrance. However, because features may be subtle, careful examination of potentially affected family members is critical to provide accurate genetic counselling and anticipatory guidance for hearing loss, renal problems, and possibly congenital heart disease.

Aetiology and genetics

Although most patients with TBS have normal chromosomes, a few have been described with cytogenetic abnormalities which have helped in the localisation of the TBS gene. A father and daughter with imperforate anus and ear anomalies had a pericentric inversion of chromosome 16 with breakpoints at p11.2 and q12.1.¹ Serville *et al.*² reported an infant with abnormal ears, triphalangeal thumbs, an incomplete imperforate anus, and a balanced translocation, 46,XX,t(5;16)(p15.3;q12.1). A 16 year old male with severe mental retardation, cupped ears with preauricular tags, severe sensorineural and conductive deafness, thumb anomalies, and low imperforate anus had a cytogenetic deletion within the long arm of chromosome 16.³ Molecular analysis of this patient found a deletion which included the distal portion of 16q12.1 and extended into 16q13.⁴ A girl with typical somatic features of TBS, developmental delay, and a complex translocation involving chromosomes 2, 11, and 16⁴³ (C M Powell, personal observation) was also found to have a deletion that extended from the middle of 16q12.1 to the middle of 16q13 (R C Michaelis, unpublished data). If one combines the regions implicated by the chromosome abnormalities in these patients, the consensus region for the TBS gene is the distal 1-1.2 Mb of band 16q12.1.⁴ This is consistent with the haplotype analysis performed on the four generation family discussed above.¹⁰⁻²⁴ Haplotype analysis of this family was consistent with the TBS gene being located in 16q12.1, between markers D16S300 and D16S415 (R C Michaelis, unpublished data).

Using a candidate gene approach, Kohlhasse *et al*⁵ found mutations in the SALL1 gene located at 16q12.1 in three affected members of a two generation family and in a sporadic case of Townes-Brocks syndrome. In the family, there was a heterozygous single base pair deletion, 1377delC, in all three affected subjects. This mutation is predicted to cause a frameshift, leading to a truncated SALL1 protein. In the sporadic case there was a heterozygous C→A mutation, which converts a serine to a stop codon. This mutation is also predicted to result in a truncated SALL1 protein.⁵

The SALL1 protein contains nine C2H2 zinc finger domains and one C2HC zinc finger domain, as well as glutamine, proline, alanine, and serine rich domains resembling those characterising the SP1 and egr families of transcription factors.⁴⁴ SALL1 is expressed in all organs affected in TBS patients, suggesting that TBS is most likely a single gene disorder. In *Drosophila*, sal is required for development of the posterior head, anterior tail segment, larval tracheal system, and adult wing. It is one of the targets of the homeotic antennapedia gene in the leg imaginal disc, and part of the hedgehog/decapentaplegic signalling cascade in the wing imaginal disc. Sal-like genes in the mouse, *Xenopus*, and medaka are expressed during development of the central nervous system, limb, or fin buds, kidney, heart, and inner ear. SALL1 is expressed during development of the fetal brain, although a specific role for it in brain development has not been specified. However, this suggests that a deficit in SALL1 function may also underlie the mental retardation seen in several TBS patients.

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